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BECKMAN COULTER, INC.
C/O DLA PIPER RUDNICK GRAY CARY US LLP
4365 EXECUTIVE DR
SUITE 1100
SAN DIEGO, CA 92121-2133

EXAMINER	
FOSTER, CHRISTINE E	
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SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/684,268	MONTERO-JULIAN ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-67* is/are pending in the application.

4a) Of the above claim(s) *20-22 and 27-67* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19 and 23-26* is/are rejected.

7)☒ Claim(s) *4,9,10,23,24 and 26* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 October 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/22/04, 8/30/04*, 5/15/06
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, claims 1-19 and 23-26 in the reply filed on 12/26/2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 20-22 and 27-67 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 12/26/2006.

Information Disclosure Statement

3. Applicant's Information Disclosure Statements filed 3/22/04, 8/30/04, and 5/15/06 have been received and entered into the application. The references therein have been considered by the examiner as indicated on the attached form PTO-1449.

4. Citations AF (WO 94/11738) and AH (WO 03/040299) have been considered only to the extent of the abstracts because they are not English language documents and only the abstracts are in English.

5. Applicant is reminded that the listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper."

Therefore, unless the references have been cited by the examiner on a form PTO-892 or cited on the above-mentioned Information Disclosure Statements, they have not been considered.

Drawings

6. The drawings are objected to because Figures 5 and 7A contain French language words. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Specification

7. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required:

Claim 9 recites that the first binding ligand may "neutravidin", or "monomeric avidin". However, the specification does not disclose the term "neutravidin" and also does not specifically refer to "monomeric avidin" but only to "avidin" *per se*. It is suggested that the specification be amended to provide proper antecedent basis for the claimed subject matter. Applicant is reminded that new matter should not be introduced into the specification.

8. The use of trademarks ("PREScission™", "StrepTactin™, Neutravidin™") has been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Objections

9. Claims 4, 9-10, 23-24, and 26 are objected to because of the following informalities:

10. Claim 4 is objected to because it recites that the solid surface "is **in**" a microtiter plate rather than that the surface "is" a microtiter plate as indicated in the specification. The specification discloses that the solid surface can be a microtiter plate [0070], i.e. that the monomer is coated in the wells of a microtiter plate.

11. Claim 9 is objected to because it appears to recite a Markush group using non-standard Markush language. The language "selected from the group consisting of" is suggested. See MPEP 2173.05(h) and 803.02.

21. Claim 10 is objected to because it refers to "a C-terminal end" but does not make clear whether this refers to a C-terminal end of the monomer or of the second binding ligand. If the claim intends to refer to a C-terminal end of the monomer, it is noted that claim 8 (from which claim 10 depends) introduces the term "the C-terminal end of the monomer", such that a similar reference to "the C-terminal end of the monomer" in claim 10 may avoid confusion.

22. Claims 23-24 are objected to because they refer to non-elected claim 22.

23. Claim 26 is objected to because it recites "a control peptide to which the MHC monomer binds in a reconstituted form", which may present confusion because the claim language does not make clear that "reconstituted form" is referring to a reconstituted form of the MHC monomer (rather than the control peptide).

Claim Rejections - 35 USC § 112

24. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

25. Claims 1-19 and 23-26 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a system comprising a "MHC monomer or modified MHC monomer" attached to a solid surface, wherein the monomer is able to denature and reconstitute

to from a ternary complex with a "suitable MHC-binding peptide" (which may also be a component of the claimed system, see claim 16). However, the genera of **"modified MHC monomers"** and **"suitable MHC-binding peptides"** are defined only by reference to functional properties. Thus, there is no indication of what structure the modified product possesses as no reference structure is provided in the claims. A skilled artisan cannot envision the detailed chemical structure of the claimed modified monomer proteins or the MHC-binding peptides.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed. The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention." MPEP 2163.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a

representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli* 872, F.2d at 1012, 10 USPQ2d at 1618.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co. The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, or chemical name', of the claimed subject matter sufficient to distinguish it from other materials." Id. at 1567, 43 USPQ2d at 1405. The court also stated that:

> a generic statement such as "vertebrate insulin CDNA" or "mammalian insulin CDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. at 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of CDNAS might be described. "A description of a genus of CDNAS may be achieved by means of a recitation of a representative number of CDNAS, defined by nucleotide sequence, falling within the scope of

the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem. Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics; i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Id. at 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

Thus, the instant specification may provide an adequate written description of the claimed genus of **modified MHC monomers** per Lilly by structurally describing representative agents or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

However, the instant specification does not describe the genus of **modified MHC monomers** in a manner that satisfies either the Lilly or Enzo standards. Although the specification discloses examples of MHC monomers, it does not disclose what portions of the MHC heavy chain can be altered, and in what way, without affecting the ability of the protein to reconstitute. Thus the identification of the genus only by reference to a functional characteristic

(ability to incorporate a peptide from solution) is insufficient for written description purposes because the specification does not disclose a correlation between structure of the modified MHC monomers and this function. In light of the substantial variance among members of this genus (which can include, for example, MHC fragments, fusion proteins, mutants, glycosylation variants, etc.), and the infinite number of different modified molecules that are encompassed, the specification fails to convey evidence of possession of the genus.

The specification also fails to adequately describe the claimed genus of **suitable MHC-binding peptides** because although it refers to examples of MHC-binding peptides, and specifies lengths of the peptides in claim 18, it does not provide sequence information for any of the peptides and does not disclose what amino acids or portions of the peptides would be responsible for binding MHC molecules. The specification discloses that the peptide preferably has "high affinity", but does not disclose sequences or specific residues that are responsible for high affinity binding. Furthermore, in the case of **modified** MHC monomers, the specification does not disclose sequences that would bind to such modified MHC monomers. In light of the substantial variance of the members of the genus of MHC-binding peptides, as disclosed for example in the instant specification at [0121], the specification fails to reasonably convey evidence of possession of the entire genus of MHC-binding peptides.

In addition, with respect to claims 13 and 17, the specification does not disclose what residues of the MHC heavy chain represent the claimed "**conformational epitope**", and accordingly does not describe what portions of the protein may be modified without destroying the epitope. Furthermore, the specification does not provide a written description of the genus of **conformational epitopes that are present in the reconstituted monomer and absent in the**

denatured monomer. The specification does not describe, for example, what residues would be exposed in reconstituted forms of MHC molecules (and in "modified" forms thereof), but inaccessible in the denatured form. Simply stating that the epitope is present in the reconstituted but not in the denatured monomer fails to convey evidence of possession since it does convey *what* such an epitope would actually look like or comprise; no structural characteristics of such epitope are described. The specification does not provide a written description either for antibodies that would bind to reconstituted, but not denatured monomers, or for epitopes on the monomers that are present in reconstituted, but not denatured monomers.

Although the specification describes the monoclonal antibody produced by hybridoma B9.12.1 as an example of an antibody having these characteristics, this single example does not adequately describe the genus of **monoclonal antibodies that specifically bind to a reconstituted monomer and not to a denatured monomer**, since the specification does not identify what specific characteristics of this antibody are responsible for this function, and therefore fails to disclose any correlation between structure and function among members of the genus.

With respect to claims 13, 15, 17-19, and 26 the specification does not describe what portions of MHC class I are responsible for binding to antibodies, beta-2 microglobulin, or to peptide, and therefore does not disclose what sequences, modifications or fragments of MHC class I molecules would retain immunological reactivity with the antibodies. In light of the large number of "modified" MHC monomers that would be encompassed by the claims, and in the absence of an identification of structural characteristics shared by the members of this genus that would still possess the recited binding properties, one skilled in the art would not envisage

possession of all modified MHC monomers that are capable of binding to antibodies, beta-2 microglobulin, and peptide.

Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genera.

26. Claims 1-19 and 23-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a system comprising one or more MHC monomers, does not reasonably provide enablement for systems comprising "modified" MHC monomers. In addition, the specification, while being enabling for a system comprising the antibody B9.12.1, does not reasonably provide enablement for all antibodies that bind to reconstituted but not denatured monomers (as in claims 13 and 17). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The nature of the invention is a system including a solid support comprising MHC heavy chain monomers or "modified" MHC heavy chain monomers. The monomers are capable of denaturing and "reconstituting" to form a ternary complex (presumably of MHC heavy chain, beta chain or beta-2 microglobulin, and peptide).

In the instant case the amount of experimentation required to practice the claimed invention is undue as the claims do not recite a specific structure for the "modified MHC monomer", only a functional characteristic (ability to "reconstitute", ability to bind to a suitable

peptide), and there is no disclosed correlation between structure and function with regard to possible modifications.

It is noted that the specification does not clearly define "**reconstituting**", which renders the scope of the claims indefinite (see rejection under 112, 2nd paragraph below). Therefore, for the purposes of ascertaining patentability under 112, 1st paragraph, the examiner has employed the broadest reasonable interpretation of the term "reconstitutes". Merriam-Webster OnLine dictionary, which defines "reconstitute" as "to constitute again or anew". Such a definition would encompass *complete* reconstitution, i.e. 100% refolding or renaturing with retention of 100% binding or other functional activity.

Although the specification indicates that MHC ternary complexes were coated onto the wells of a microplate, denatured, and subsequently "reconstituted" with high affinity peptide (see p. 34-35), there is no indication that this system resulted in 100% properly refolded MHC monomers with full retention of binding activity.

The prior art teaches that the denaturing and renaturing (refolding) of proteins is an unpredictable process that rarely, if ever, can be accomplished with 100% efficiency. Rather, refolding is known to be a highly empirical process that often results in the majority of the protein aggregating or failing to reconstitute into the properly folded conformation. For example, Garboczi et al. refolded the MHC class I molecule HLA-A2 into ternary complexes; however, the yield of successfully reconstituted (refolded) protein was only 10-15%, while the remainder (85-90%) was misfolded or aggregated material that thus could not be reconstituted (Garboczi et al., *Proc. Natl. Acad. Sci USA* 89 (1992), 3429-3433, see especially the abstract and p. 3431). Thus, the prior art fails to teach that MHC molecules can be completely reconstituted after

denaturation (100% of the starting molecules successfully refolded). Because the specification does not clearly indicate what would be meant by a MHC monomer that "reconstitutes", the claims are being interpreted as broadly encompassing systems in which all MHC molecules have the ability of completely reconstituting, which is not enabled in view of the prior art.

With respect to the recited "**modified** MHC monomers", predicting which potential changes can be tolerated in a protein's amino acid sequence without affecting a desired activity requires a sophisticated knowledge of and guidance with regard to which amino acids in the proteins' sequence, of any, are tolerant of modification and which are conserved (for example, expectedly intolerant to modification), and a detailed knowledge of the ways in which the protein's structure relates to its function. In the instant case, the necessary guidance has not been provided in the specification. Therefore, while it is known in the art that many amino acid substitutions are possible in any given protein, the positions within the protein's sequence where such substitutions can be made with a reasonable expectation of success are limited, as certain positions in the sequence are critical to the protein's structure/function relationship. It is also known in the art that a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many cases. For example, various sites or regions directly involved in binding activity and in providing the correct three-dimensional spatial orientation of binding and active sites can be affected (see Wells, Biochemistry, Vol. 29 (1990), pages 8509-8517).

Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of

the protein. Burgess et al. *J Cell Bio.* 111:2129-2138, 1990. In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity, yet replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. Lazar et al. *Molecular and Cellular Biology* 8:1247-1252 (1988). Similarly, it has been shown that glycosylation of antibodies reduces the resistance of the antibodies to proteolytic degradation, while CH2 deletions increase the binding affinity of the antibodies. See Tao et al., *The Journal of Immunology*, 143:2595-2601 (1989). Seffernick et al. (J. Bacteriology, Vol. 183, pages 2405-2410, 2001) disclose two peptides having 98% sequence identity and 99% sequence identity, differing at only 9 of 475 amino acids (p. 2407, right column, middle and p. 2408, Fig. 3). The polypeptides of Seffernick et al. are identical along relatively long stretches of their respective sequences (p. 2408, Figure 3). However, the polypeptides exhibit distinct functions. The modifications exemplified in the reference are small compared to those contemplated and encompassed by "modified" monomers of the claimed invention.

These various references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristics of a protein.

The instant specification provides no working examples of any **modified MHC monomer** that is encompassed by the claims. It is no way predictable that randomly selected mutations, such as deletions, substitutions, etc. in the disclosed sequences would result in a protein having the claimed ability to reconstitute. Given the fact that MHC molecules themselves are extremely polymorphic (i.e. there are many different naturally occurring versions of these

molecules in the population), it is evident that the genus of "modified" MHC molecules is of even greater breadth.

With respect to the **suitable MHC-binding peptides** claimed (see especially claim 18), the specification discloses preferred lengths of the peptides [0074] and examples of peptides by name [0119]. However, given the breadth of "a suitable HLA-binding peptide of from about 8 to about 12 amino acids" as in claim 18, the lack of guidance with regard to preparation of such peptides that would have the desired binding specificities (particularly with regard to binding to "modified" MHC monomers), and in light of the above-mentioned unpredictability associated with even minor changes to amino acid sequences, the guidance in the specification is not commensurate with the scope of the claims.

Furthermore, prior art recognizes that as a result of the above-mentioned MHC polymorphism, each MHC molecule has its own specificity characteristics, which could only be determined experimentally at the time of the invention (see Pederson et al., WO 00/15665, at p. 6). Buus et al. (Current Opinion in Immunology 1999, Vol. 11, p. 209-213) describe efforts to predict peptide-MHC binding, referring to the "extreme polymorphism" as a "huge logistic challenge to the experimentalist" (p. 209, right column). The reference concludes that despite recent advances in the ability to predict peptide binding, the field is still in need of improvements (p. 212, left column, the last paragraph).

As a result, in order to carry out the claimed invention in its full scope, one skilled in the art would need not only to generate and screen the large number modified MHC molecules encompassed by the claims, but also to synthesize the large number of 8-12 amino acid peptides

and screen these for the ability to bind to MHC and/or modified MHC monomers, which would clearly present an undue burden of experimentation.

Although recombinant and mutagenesis techniques are known in the art, it is not routine in the art to screen large numbers of mutated or otherwise modified proteins/peptides where the expectation of obtaining a desired activity is unpredictable. The specification provides guidance of a general nature with respect to different modified MHC monomers that may be prepared (see p. 12-16). However, this teaching does not present specific structures, and there are working examples of modified MHC monomers. The specification suggests that "[t]he effect of any particular modification can be evaluated by routine screening in a suitable assay for the desired characteristic" [0046]. However, such a statement merely amounts to an invitation to conduct further research in light of the large quantity of experimentation necessary to generate the infinite number of modifications encompassed by the claims and to screen the same for activity.

This "make and test" position is inconsistent with the decisions of *In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)* where it is stated that "...scope of claims must bear a reasonable correlation to scope of enablement provided by the specification to persons of ordinary skill in the art...". Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See *In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 Fed. Cir. 1998).*

With respect to the anti-MHC class I monoclonal antibody having the characteristics recited in claims 13 and 17 (specifically binds to reconstituted monomer and not to denatured monomer), the specification's teaching of the monoclonal antibody produced by hybridoma

B9.12.1 is not a teaching that is commensurate in scope with the claims, particularly in light of the breadth of the claims. Since the specification has not adequately described the genus of modified MHC monomers, the specification similarly fails to describe the genus of antibodies that would bind to these molecules.

Thus, in light of the breadth of the claims, the state of the prior art which fails to teach complete reconstitution of MHC molecules, the unpredictability associated with modifying protein and peptide sequences while retaining desired biological characteristics, and the lack of working examples of modified MHC monomers, the specification fails to teach the skilled artisan how to make and use the claimed invention without undue experimentation.

27. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

28. Claims 1-19 and 23-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

29. Claim 1 recites a "**suitable** MHC-binding peptide", which renders the claim indefinite because the metes and bounds of the claim are unclear. Similarly, claim 18 refers to "a **suitable** HLA-binding peptide". The specification does not clearly define what peptides would be considered "suitable". It is unclear what peptides would be considered "suitable" (and for what purpose) vs. those that would be "unsuitable".

30. Claim 1 recites that "the surface has attached thereto **one or more** MHC monomer or modified MHC monomer, wherein **the monomer** denatures...". The claim is indefinite because

it is unclear whether the reference to "one or more" MHC monomers means that one or more *molecules* of an MHC monomer are present on the surface, or alternatively whether an array of different *types* of MHC monomers is present. The reference to "the monomer" in the singular also may present confusion since if multiple monomers and/or different types of monomers are present, it is unclear which species are being referred to as "the monomer".

31. Claims 2, 11, 14, and 18 recite "**reconstituting conditions**", "**denaturing conditions**", and/or "**renaturing conditions**", which are indefinite because the specification does not provide limiting definitions for the terms. The specification discloses at [0079] that "renaturing conditions typically include the presence of a suitable MHC binding peptide for the monomer, the presence of beta-2 microglobulin, and a suitable refolding buffer having a pH of about 7 to about 8.5". However, this instance of exemplification does not amount to a specific definition of "reconstituting conditions". Similarly, the specification sets forth an example of what "denaturing conditions" would include [0079] but does not provide a limitation definition for this term. It is not clear what conditions would be encompassed by "reconstituting," "denaturing," or "renaturing" according to the claims and consequently, the metes and bounds of the claims are unclear. It is also unclear how "reconstituting conditions" differ from "renaturing conditions" as the specification appears to employ these terms synonymously.

32. Claim 11 recites that the monomer "**reconstitutes**". Similarly, claims 13, 17-18, and 26 refer to a "reconstituted monomer" or "reconstituted form" of a monomer. The specification does not clearly define the term "reconstitutes", such that the metes and bounds of the claims are unclear. It is unclear what would be considered to be a "reconstituted" monomer.

33. Claim 5 recites that the solid surface is "**suitable for screening in a high throughput system**", which is indefinite because the claim does not recite any additional *structural or functional* limitations of the solid surface, and the specification does not clearly disclose what structural or functional properties would impart the desired property of being suitable for high-throughput screening. It is unclear how a solid surface suitable for high-throughput screening would be distinguished from one that is unsuitable for this purpose, and therefore, it is unclear what additional limitations or properties of the solid surface are being invoked by the claim.

34. Claim 14 recites the limitation ""the reconstituting conditions" in line 1. There is insufficient antecedent basis for this limitation in the claim.

35. Claim 8 rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: **attachment** of the second binding ligand to the C-terminal end of the monomer. The claim recites that the C-terminal end of the monomer is "provided with" a second binding ligand (which may be biotin), and that the solid surface is coated with a first binding ligand (such as avidin). However, the specification discloses that in such embodiments, the second binding ligand must be "connected to or within" the MHC monomer, e.g. by covalent or noncovalent bond" [0084]. If biotin were merely "provided with" the MHC monomer as a separate reagent rather than being bound to the monomer, there would be no way for the MHC monomer to bind to the first binding ligand on the solid surface; therefore, attachment is essential.

36. Claim 9 contain the trademark/trade names Neutravidin™ and StrepTactin™. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe two recombinant proteins; accordingly, the identification/description is indefinite since there is no evidence of record to indicate that the recited trademarks uniquely identify the proteins.

37. Claim 19 is indefinite in the recitation of "**B9.12.1**" because the characteristics of this hybridoma are not known. The use of " B9.12.1" as the sole means of identifying the claimed reagent renders the claim indefinite because this is merely a laboratory designation that does not clearly define the claimed product. Furthermore, different laboratories may use the same laboratory designations to define completely distinct cell lines/hybridomas. Amending the claims to recite the appropriate ATCC Accession Number would obviate this rejection.

Claim Rejections - 35 USC § 102

38. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

39. Claims 1-5, 8-12, and 14-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Altman et al. (US 5,635,363).

Altman et al. teach a system comprising a solid surface (e.g., beads or microtiter plates) attached to one or more MHC monomer or modified MHC monomer ("multimeric binding complex" of MHC protein subunits and peptide antigen). See the entire document, especially the abstract; column 2, lines 51-54; column 3, line 19 to column 5, line 7 to column 6, lines 51-65; and column 8, lines 4-58). The examiner notes that the multimeric binding complex of Altman et al., comprising MHC class I chain (monomer) in complex with beta-2 microglobulin and peptide (see especially at column 3, lines 19-32) reads on the claimed system because claim 1 employs open transitional language ("comprising"). Altman et al. teach various modified MHC monomers, including a single-chain heterodimer in which the alpha and beta subunits are fused together as a single polypeptide monomer (column 4, lines 21-33).

Regarding the limitation that the monomer incorporates from solution a suitable MHC-binding peptide, the system of Altman et al. would also be capable of performing this intended use since the reference teaches all recited structural limitations of the claim.

With respect to claims 4-5, Altman et al. teach that the multimeric binding complex may be attached to microtiter plates, which enable a large number of assays to be carried out simultaneously (column 8, lines 27-49).

With respect to claims 8-10, Altman et al. teach systems comprising a solid surface (agarose beads) coated with a first binding ligand (streptavidin), which are then bound to a biotinylated MHC class II heterodimer (see column 13, line 40 to column 14, line 31). Biotin is attached to the MHC

monomer at the MHC C-terminus to avoid potential hindrance of at the antigenic peptide site (see column 13, lines 4-19 and column 6, lines 18-33).

With respect to claims 11-12 and 14, it is noted that the limitations refer to the intended use of the claimed product. Since Altman et al. teach the same reagents (e.g. HLA class I) as disclosed in the instant specification, they would be capable of performing the recited intended uses of denaturing and reconstituting as claimed.

With respect to claims 15-16, the MHC monomer may be HLA class I and the system may further comprise beta-2 microglobulin (see especially column 3, lines 19-46).

Claim Rejections - 35 USC § 103

40. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

41. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

42. Claims 6-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Altman et al. in view of Becker et al. (US 6,485,913).

Altman et al. is as discussed above, which teaches a system substantially as claimed but which fails to specifically teach that the monomer is attached reversibly or by a cleavable linkage.

Becker et al. teach immobilization of reagents to solid supports, in which proteins (for example) can be immobilized reversibly, for example by using a selectively cleavable linker that allows for cleavage under defined conditions (column 17, line 1 to column 19, line 17). Becker et al. also teach reversible immobilization of proteins via free thiol groups, which has the advantage in that thiols can be blocked to temporarily prevent reaction (see column 19, lines 1-17).

Therefore, it would have obvious to one of ordinary skill in the art to employ reversible immobilization as taught by Becker et al. in order to allow for the immobilized MHC monomer to be released from the solid support under defined conditions. One would have a reasonable expectation of success because Altman et al. teach that the MHC monomer can be attached to the surface by any convenient means, and that the particular manner of binding is not crucial (column 8, lines 28-35).

43. Claims 13 and 17-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Altman et al. in view of Jager et al. (*The Journal of Immunology* (March 2002), p. 2766-2772).

Altman et al. is as discussed above, which teaches a system substantially as claimed. However, the reference fails to specifically teach that the system includes a monoclonal antibody that binds to the reconstituted, but not the denatured form of the MHC monomer.

However, Jager et al. teach methods for detecting interactions of T cells with MHC molecules, in which the monoclonal antibody w6/32 is employed in order to ensure that an equal number of MHC/peptide complexes are used in the assay (see especially the abstract and p. 2767, the left column). The w6/32 antibody recognizes reconstituted, but not denatured class I antibody since it recognizes a monomorphic determinant in the correctly folded ternary complex. This antibody therefore recognizes a "conformational epitope" as in claim 13 since the epitope is found only in the correctly folded conformation.

Therefore, it would have been obvious to one of ordinary skill in the art to include the w6/32 monoclonal antibody taught by Jager et al. in the system of Altman et al. for the purpose of detecting MHC/peptide complexes to be used in a T cell detection assay, so that an equal number can be used, which is particularly relevant because the system of Altman et al. is intended for the purpose of detecting T cells (see column 8, lines 17-26).

With respect to claim 18, the system of Altman et al. includes suitable peptide of 8-10 amino acids in the case of class I MHC proteins (column 3, lines 20-32; column 2, lines 29-40; column 4, line 63 to column 5, line 47).

44. Claims 13 and 17-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Altman et al. in view of Hildebrand et al. (US 2003/0166057 A1).

Altman et al. is as discussed above, which teaches a system substantially as claimed. However, the reference fails to specifically teach that the system includes a monoclonal antibody that binds to the reconstituted, but not the denatured form of the MHC monomer (which may be HLA class I).

Hildebrand et al. also teach the monoclonal antibody W6/32, which binds to a conformational epitope in class I MHC molecules that includes both the heavy chain and beta2m ([0276], this antibody is also discussed in the Jager et al. reference above). The reference teaches that the antibody can be used in order to test for conformationally intact ternary complexes (trimers) [0317]-[0321]. This antibody therefore recognizes a "conformational epitope" as in claim 13 since it specifically binds to conformationlly intact complexes.

Therefore, it would have been obvious to include the monoclonal antibody W6/32 in the system of Altman et al. as a control reagent for the purpose of ascertaining whether the multimeric ternary complexes are conformationally intact.

With respect to claim 18, as noted above, the system of Altman et al. includes suitable peptide of 8-10 amino acids in the case of class I MHC proteins (column 3, lines 20-32; column 2, lines 29-40; column 4, line 63 to column 5, line 47).

45. Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Altman et al. in view of Jager et al., or, alternatively, Altman et al. in view of Hildebrand et al., and further in view of Marin et al. (*Hybridoma* Vol. 14 (1995), 443-451, Applicant's IDS of 8/30/04).

Altman et al., Jager et al., and Hildebrand et al. are as discussed above, which teach a system including a monoclonal antibody that binds to the reconstituted, but not the denatured form of class I MHC. However, the references fail to specifically teach the antibody produced by hybridoma B9.12.1.

The antibody produced by hybridoma B9.12.1 was well known in the art at the time of the invention for the purpose of detecting class I MHC molecules. See Marin, in particular the

abstract and p. 444, left column, the first full paragraph. The reference teaches that the B9.12.1 monoclonal antibody binds to a monomorphic determinant of MHC class I molecules that has already been used with success in cell-targeting experiments, and that also is commonly used for phenotyping human cells, and therefore allows for easy monitoring of its binding capability.

Therefore, it would have been obvious to one of ordinary skill in the art to employ the B9.12.1 antibody of Marin in place of the W6/32 antibody (taught in both Jager and Hildebrand) in the system of Altman and Jager, or alternatively, Altman and Hildebrand because Marin teaches that the B9.12.1 antibody allows for easy monitoring of binding capability. One would have a reasonable expectation of success because Marin teaches that the B9.12.1 antibody also recognizes human MHC class I molecules.

Furthermore, the Courts have ruled that art-recognized equivalence between embodiments provides a strong case of obviousness in substituting one material for another.

In regards to the instant application, the specification teaches that any monoclonal antibody that specifically binds to a conformational epitope present only in a ternary complex of an MHC monomer and does not set forth a reason for choosing one monoclonal antibody over another. See [0087].

Because the B9.12.1 antibody taught by Marin et al. is recognized as an equivalent applied for the same purpose, and Applicants have not provided evidence indicating why these two antibodies may not be considered art-recognized equivalents, it would have been obvious to one of ordinary skill in the art at the time of the invention to substitute the monomorphic, anti-MHC class I monoclonal antibody B9.12.1, as taught by Marin et al., for the monomorphic, anti-MHC class I monoclonal antibody W6/32 of Hildebrand in the system of Altman et al. and

Hildebrand because Hildebrand teaches that monomorphic monoclonal antibodies are particularly useful for identifying and characterizing MHC molecules, and in light of the teaching of Marin that B9.12.1 is also a monomorphic monoclonal antibody useful for this same purpose. Similarly, it would have been obvious to employ the B9.12.1 antibody in place of the W6/32 antibody of Jager et al. in the system of Altman et al. and Jager et al. because the both antibodies were known in the art to be useful for the same purpose of detecting class I MHC molecules.

46. Claims 23-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Altman et al. in view of Zuk et al. (US 4,208,479).

Altman et al. is as discussed above, which teaches a system substantially as claimed but which fails to specifically teach a "kit" comprising the system. The reference also fails to specifically teach that the monomers are in dried form.

With respect to claim 23, Zuk et al. that reagents for performing assays may be provided in dry form (column 2, lines 49-54; column 22, lines 36-39). It is asserted that the advantages of dried forms of reagents, specifically their stability or shelf-life and their convenience over wet reagent forms, was well known in the art at the time of the invention.

Therefore, it would have been obvious to one of ordinary skill in the art to provide the system of Altman et al. in dried form as taught by Zuk et al. for convenience and/or improved stability.

With respect to claim 24, Zuk et al. teach that in performing assays it is a matter of substantial convenience to provide the needed reagents combined in a kit (column 22, lines 20-68). The reference teaches that kits can also provide significant enhancement in accuracy.

Therefore, it would have been obvious to one of ordinary skill in the art to provide the system of Altman et al. in kit form for convenience as taught by Zuk et al. One would have a reasonable expectation of success because Altman et al. teach that the system is intended to be employed in assays, including immunoassays (see e.g. at column 7, line 56 to column 8, line 49).

47. Claims 25-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Altman et al. in view of Zuk et al. as applied to claim 24 above, and further in view of Schutzer et al. (US 5,187,065).

Altman et al. and Zuk et al. are as discussed above, which fail to specifically teach an "instruction" for a kit. However, it was well known in the art at the time of the invention to provide instructions as part of a kit for the purpose of instructing the kit user how to carry out assays with the kit. For example, see Schutzer et al. at column 3, lines 40-57.

Therefore, it would have been obvious to one of ordinary skill in the art to include an instruction in the kit of Altman et al. and Zuk et al. for the purpose of instructing the user how to use the kit. It is further noted that where the only difference between a prior art product and a claimed product is printed matter that is not functionally related to the product, the content of the printed matter will not distinguish the claimed product from the prior art. In re Ngai, 367 F.3d 1336, 1339, 70 USPQ2d 1862, 1864 (Fed. Cir. 2004). See MPEP 2112.01.

With respect to claim 26, Altman et al. teach that the system may include a bound peptide antigen (see for example claim 3, lines 7-32; column 4, line 63 to column 5, line 47). This meets the

claimed limitation of being a "control peptide" in the absence of a recitation of any limitations that would distinguish the peptide from that of Altman et al. As such, when providing the system of Altman et al. in kit form (as taught by Zuk et al.) it would have been clearly obvious to include the peptide of Altman since this is one of the components of the system.

Double Patenting

48. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

49. Claims 1-19 and 23-26 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-78 of copending Application No. 10/782,664. Although the conflicting claims are not identical, they are not patentably distinct from each other because Application No. 10/782,664 also claims a system comprising an MHC monomer or modified MHC monomer (see for example claims 73-78). The MHC monomer may be attached to a solid phase (claims 8 and 78). The MHC monomer of the

system of Application No. 10/782,664 is also capable of incorporating a suitable MHC-binding peptide from solution in that it is capable of binding to added "tracer-tagged MHC-binding peptide" (see for example claim 23 and 73).

50. Claims 1-19 and 23-26 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-21 of copending Application No. 10/269,473. Although the conflicting claims are not identical, they are not patentably distinct from each other because Application No. 10/269,473 also claims a system comprising an MHC monomer or modified MHC monomer attached to a solid surface (see for example claim 1). The system of Application No. 10/269,473 is also capable of incorporating from solution a suitable MHC-binding peptide since it binds to such a peptide under reconstituting conditions (see for example claims 16 and 21).

The above are provisional obviousness-type double patenting rejections because the conflicting claims have not in fact been patented.

Conclusion

51. No claims are allowed.

52. It is noted that this Office Action contains rejections of the same claims under 35 USC 112, 1st (scope of enablement) and 35 USC 102(b)/103(a). While these rejections may seem contradictory, they are not, because each is based upon a different legal analysis, i.e., sufficiency of the disclosure of the instant application to support claims under 35 USC, 1st paragraph vs. sufficiency of a prior art disclosure to anticipate or render obvious an embodiment(s) of the claimed invention (See *In re Hafner*, 161 USPQ 783(CCPA 1969)).

53. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Cai et al. (US 6,225,042 B1), Moghaddam (US 5,514,557), Humphreys et al. (US 5,919,639, see for example Table 39 and legend), Burrows et al. (US 6,270,772 B1, especially column 19), and Tidey et al. (US 6,046,013) also teach immobilizing MHC molecules to solid supports.

Ekins (US 5,599,720), Hackett et al. (US 5,759,774), Weiss et al. (US 4,912,030), Reynolds (US 4,017,597) and Thomas et al. (US 2002/0106708 A1) are cited in relation to claim 23 for their teaching of the improved stability and/or convenience of dry-format reagents, including polypeptides.

Skerra et al. (US 6,103,493) and Bachovchin et al. (US 5,965,532) is cited with respect to claim 9, for teaching of modified streptavidin and monomeric avidin, respectively.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 8:30-5. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached at (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Christine Foster, Ph.D.
Patent Examiner
Art Unit 1641

LONG V. LE 02/01/07
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600